

REMARKS/ARGUMENTS

By this Amendment, claim 19 is amended. Claims 12-18 have been withdrawn from consideration pursuant to a restriction requirement. Claims 1-20 are pending. Citations to the Specification are directed to U.S. Patent Application Publication No. 2005/0182114 (Parthasaradhi). Support for the amendment to claim 19 adding the limitation wherein the crystalline form is stable, can be found throughout the Specification as filed, and specifically in ¶[0005]

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Reconsideration of the restriction requirement is respectfully requested.

Restriction Requirement

Applicants hereby affirm their prior election with traverse of Group I, claims 1-11 and 19, reserving their rights under 35 USC § 121 to file a divisional application for the nonelected claims.

Rejection under 35 USC § 112 second paragraph

Claims 3-4 and 8-9 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is respectfully traversed.

The Examiner argues that claims 4 and 9, line 2, respectively recites the limitation "figure 1" or "figure 2", and that they therefore fail to particularly point out and distinctly claim the subject matter which applicant regards as the invention. However, incorporation by reference to

a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993). MPEP 23173.05(s). Here, the claims are incorporating the X-ray powder diffraction pattern as set forth in Figures 1 and 2. There is not a more concise way to incorporate the data from the X-ray powder diffraction pattern, other than to incorporate the Figures by reference. Since it would be unwieldy to duplicate the Figures into the claims, reconsideration and withdrawal of the rejection is respectfully requested.

The Examiner argues that claims 3 and 8 respectively recite X-ray powder diffraction pattern data, and that it is unclear what is the difference of the compound candesartan cilexetil 1,4 -dioxane solvate of claim 3 and 8. The Examiner inquires as to whether they the same candesartan cilexetil 1,4 -dioxane solvate compound. However, they are different polymorphic forms of candesartan cilexetil 1,4 dioxane, each characterized by a different X-ray powder diffraction pattern and therefore the metes and bounds of the claims have been fully defined. Accordingly reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 112 first paragraph

Claim 19 stands rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner argues that it is well recognized in the art that process of preparing pharmaceutical composition will produce the thermodynamically stable form of crystals, thus: the instant Form II, after mixing, grinding, compressing would be

transformed into a thermodynamically stable form(s), citing Brittain's publication, pages 348-361. This rejection is respectfully traversed.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. United States v. Teletronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

Here, the claim is enabled because there is not any reason to doubt the objective truth of the statements contained in the Specification for enabling support. The Specification discloses the manner and process for making and using the claimed invention, including examples which show the efficacy of the claimed invention. Applicants disclose a novel 1,4-dioxane solvate of candesartan cilexetil and two novel crystalline forms of candesartan cilexetil ¶[0004]. In Example 1, Applicants disclose a method of producing candesartan cilexetil solvate ¶[0019]. In Example 2, Applicants disclose a method of producing candesartan cilexetil form III ¶[0020]. In Example 4, Applicants disclose a method of producing candesartan cilexetil form IV ¶[0022].

Thus, given the teachings of the Specification, in light of the further experimentation carried out by the Applicant using the disclosed methods, the quantity of experimentation required is not excessive in view of the subject matter of the claims. The Specification sets forth several methods for producing the novel 1,4-dioxane solvate of candesartan cilexetil, and the two novel crystalline forms of candesartan cilexetil. Working Examples are also provided, as well as detailed information as to the methods. This information can be used by one of ordinary skill in the art to determine appropriate solution conditions make and use the claimed invention, without undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection of pending claim 19 as lacking enablement is respectfully requested.

Prior Art Rejections

The Examiner argues that the prior art reference of Naka et al. US 5,196,444, while not providing applicants' instant X-ray diffraction data names crystalline form of candesartan cilexetil solvate, and further argues that as these forms differ from the claims in that the references are silent on the X-ray diffraction data or the crystalline form, applicants must show that their crystalline form really is different from any of the ones prepared in the prior art citing In re Best.

However, if the Examiner is arguing that the ' 444 Naka patent inherently discloses the crystalline form of candesartan cilexetil as instantly claimed, then the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed.

Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, the Examiner has not met that burden by arguing that Applicant needs to show the absence of an alleged effect. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

If the Examiner is aware of, or alleges to have some knowledge that the crystalline form of candesartan cilexetil disclosed by Naka et al. are the novel 1,4-dioxane solvate of candesartan cilexetil, or the two novel crystalline forms of candesartan cilexetil, then the Examiner should provide such knowledge. It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art. In re Ahlert, 424 F.2d at 1091, 165 USPQ at 420-21. If applicant adequately traverses the examiner's assertion of official notice, the examiner must provide documentary evidence in the next Office action if the rejection is to be maintained. See 37 CFR 1.104(c)(2).

See also In re Zurko, 258 F.3d at 1386, 59 USPQ2d at 1697 ("[T]he Board [or examiner] must point to some concrete evidence in the record in support of these findings" to satisfy the substantial evidence test). If the examiner is relying on personal knowledge to support the finding of what is known in the art, the examiner must provide an affidavit or declaration setting forth specific factual statements and explanation to support the finding, pursuant to 37 CFR 1.104(d)(2).

However, there is no basis for this assumption. The use of different solvents will produce different crystalline forms of a product. For example, U.S. Patent Application Publication No. 2004/0102523 (Broquaire et al.) is directed to a process for obtaining crystalline forms of the enantiomers of modafinil, and the crystalline forms which it is possible to obtain according to this process. The '523 publication discloses that "[i]n this method, the nature of the solvent selected and the conditions of crystallization selected can be used to direct the preparation of any of the polymorphic forms. Crystallization solvents and conditions will be disclosed hereinafter for each modafinil form, respectively I, III, IV and VII obtained according to this method" ¶[0109]. Therefore, the assumption that crystallization from 1,4-dioxane will yield the same polymorphic form as crystallization from methanol, ethanol, isopropyl alcohol, ketone, etc. has no basis in fact.

Rejection under 35 USC § 102(b)

Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Naka et al. US 5,196,444. This rejection is respectfully traversed.

The Examiner argues that the '444 Naka patent discloses a pharmaceutical composition

comprising a compound candesartan cilexetil and a pharmaceutical acceptable diluent (i.e., solvent 1,4 -dioxane) or carrier (i.e., aqueous solution), see column 10, lines 54-60, and that an acceptable carrier can be water and therefore the instant crystal forms of the instant compound dissolves in the composition (i.e., aqueous solution), and it will exist in free form and not as a crystal form or a solvate form.. In Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". The claim is drawn to a pharmaceutical composition wherein candesartan cilexetil Form III is used. In the instant case, not every element of the claims is present in the '444 Naka patent.

However, the instant claim is directed to a pharmaceutical composition comprising candesartan cilexetil form III in stable crystalline form. The '444 Naka patent does not disclose this specific polymorph as claimed by Applicant. The examiner failed to demonstrate that the prior art even recognized that the claimed compound exists in different polymorphic forms, or that there is a known or obvious way to manufacture the specific polymorphic form claimed. No polymorphs of candesartan cilexetil dioxane solvate are disclosed in the '444 Naka patent. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency,

the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' "In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, the Examiner has assumed, without providing any evidence, that the crystalline form of candesartan cilexetil of the '444 Naka patent is the same form as instantly claimed. However, there is no basis for this assumption.

As set forth above, the use of different solvents will produce different crystalline forms of a product. For example, U.S. Patent Application Publication No. 2004/0102523 (Broquaire et al.) is directed to a process for obtaining crystalline forms of the enantiomers of modafinil, and the crystalline forms which it is possible to obtain according to this process. The '523 publication discloses that "[i]n this method, the nature of the solvent selected and the conditions of crystallization selected can be used to direct the preparation of any of the polymorphic forms. Crystallization solvents and conditions will be disclosed hereinafter for each modafinil form, respectively I, III, IV and VII obtained according to this method" ¶[0109]. Therefore, the assumption that crystallization from 1,4-dioxane will yield the same polymorphic form as crystallization from methanol, ethanol, isopropyl alcohol, ketone, etc. has no basis in fact.

In addition, the claim is directed to a pharmaceutical composition comprising a stable crystalline form, and thus the claimed pharmaceutical composition is not disclosed in the '444 Naka patent.

Accordingly, reconsideration and withdrawal of the rejection of claim 19 under 35 USC 102(b) is respectfully requested.

Rejection under 35 USC § 103(a)

Claims 1-11 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naka et al. US 5,196,444 in view of Brittain's publication, polymorphism in Pharmaceutical Solids, Drugs and the Pharmaceutical Science; 1999, V. 95, pages 348-361. This rejection is respectfully traversed.

The Examiner argues that the '444 Naka patent in view of the Brittain reference teaches or suggests various crystal forms of candesartan cilexetil using various solvents, and that one would be motivated to employ the compounds/compositions of Naka et al. to obtain the instant crystalline form of the same compound candesartan cilexetil or its solvate or solvent form and its pharmaceutical compositions, wherein the instant compound is in a crystalline form (i.e., form III). The Examiner further argues that changing the form, purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity or characteristic was inherent in or rendered obvious by the prior art, citing In re Cofer. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of

success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), MPEP 2143.

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). MPEP 2143.03.

In the instant case, not every element of the claims is taught or suggested in the combination of the '444 Naka patent and the Brittain reference. The instant claims are directed to a novel 1,4-dioxane solvate of candesartan cilexetil and two novel crystalline forms of candesartan cilexetil. However, the prior art relied upon by the examiner does not teach or suggest the specific polymorphs as claimed by Applicant. The examiner failed to demonstrate that the prior art even recognized that the claimed compound exists in different polymorphic forms, or that there is a known or obvious way to manufacture the specific polymorphic form claimed. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic (see above). Here, the Examiner has assumed, without providing any evidence that the methods of producing candesartan cilexetil in the '444 Naka patent can be altered to produce the claimed polymorphs. However, there is no basis for this assumption because, as set forth above, the use of different solvents will produce different crystalline forms of a product (see U.S. Patent Application Publication No. 2004/0102523 (Broquaire et al.)). Therefore, the assumption that crystallization

from 1,4-dioxane will yield the same polymorphic form as crystallization from methanol, ethanol, isopropyl alcohol, ketone, etc. has no basis in fact.

In addition, there is no motivation for one of skill in the art to alter the methods of the '444 Naka patent to arrive at the claimed method, and no reasonable expectation of success. There is no teaching or suggestion within the '444 Naka patent to alter the method as taught by the '444 Naka patent to arrive at the instantly claimed method. The Examiner argues that the motivation is that the skilled artisan would be motivated to employ the process taught by the '444 Naka patent to crystallize candesartan cilexetil and expect to obtain the desired product because he would have expected the analogous solvents and solute to behave similarly. However, the '444 Naka patent does not disclose or suggest methods of preparation of candesartan cilexetil crystalline forms wherein the solvent is 1,4-dioxane. Since the reference does not disclose or suggest this, there is no motivation to employ the process taught by the '444 Naka patent to crystallize candesartan cilexetil and expect to obtain the desired product to reach the limitations of the claims, and no expectation of success.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-11 and 19 under 35 USC 103(a) is respectfully requested.

Claim Objections

Claims 1-6 and 19 are objected to as depending on a non-elected subject matter. This rejection is respectfully traversed. Claim 19 has been amended to be limited to candesartan cilexetil form III in stable crystalline form. Claims 1-6 are directed to a candesartan cilexetil 1,4-dioxane solvate and form III of candesartan cilexetil. Reconsideration and withdrawal of the

objection is respectfully requested.

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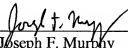
For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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